scious people are unable to protect their airways and therefore those who care for such persons must provide the protection. This is a demanding responsibility and has resulted in many rules and procedures designed to minimize or prevent occurrence of aspiration pneumonitis. The rules demonstrate once again that good medical care, like virtue and respect, cannot be legislated.

As noted, the Ruggera and Taylor article is a review, and it presents no new information. Nonetheless, one could quarrel with the authors' uncontroversial presentation of some controversial matters, such as the role of steroids in treatment, the ineffectiveness or harmfulness of saline lavage, the degree of effectiveness of prophylactic gastric alkalization and the importance of atropine. These points are probably of limited importance, however, if proper management and awareness can be accomplished.

Why does aspiration pneumonitis persist in the presence of repeated warnings and development of several methods effective in prevention? Why does it still occur where trained personnel administer anesthesia? These rhetorical questions defy precise answer but do promote speculation. The incidence of this problem has almost certainly reduced sharply in recent decades. In many institutions, it is a rare occurrence in spite of an increasing number of opportunities for it to happen. The repeated reviews and warnings have been effective.

There is reason to believe that a most important factor related to incidence of this complication still is lack of expertise in management. For example, it is possible that the prevalence of the problem in obstetrical patients is as much due to poor coverage of obstetrical anesthesia as to factors particular to such patients. Some of the preventive measures—such as awake untubation and rapid induction techniques—are dependent on at least a modicum of operator skill and may therefore be inadequately accomplished or actually avoided by those less expert. The less conscientious may be lulled into a state of some complacency by the *almost* routine successful induction.

It is to be hoped that awareness of the problem will increase, for this will provide effective protective action. No additional methods are in fact necessary—if we use what we have.

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Treating Breast Carcinoma

THE SUBJECT of this month's Medical Staff Conference is advances in the treatment of carcinoma of the breast. Also in this issue are two articles dealing with breast reconstruction after surgical operation for breast cancer.

Breast cancer is a disease that currently is highly visible to the public. In both the printed press and the electronic media, reports abound about controversies and exciting results related to breast cancer in such areas as screening, detection, treatment and rehabilitation. In the 80 years since Halsted first described radical mastectomy, the treatment of breast cancer has remained a subject of strong controversy and weak data. Diverse proposals of new therapeutic regimens have been received with the often justified criticism that the population under survey was unrepresentative because of excessive selectivity and that findings were nonreproducible because of unsatisfactory examination, improper because of defective classification or insignificant because of small numbers.

Today the new exciting development is the adjuvant treatment with drugs of women after mastectomy. The hypothesis behind this combined modality approach is that in many cases breast cancer has microscopically disseminated outside of the range of the surgical knife at the time of diagnosis.[1] The microscopic involvement of the regional lymph nodes with tumor is currently considered the strongest indicator of this dissemination. It has been shown in reported studies that when there are positive nodes in mastectomy specimens the chance of recurrence is high. Since chemotherapy can kill tumor cells anywhere in the body and is effective against clinically evident metastatic breast cancer it has become the prime candidate to combine with locally eradicative therapy.

In 1972 the National Cancer Institute launched a large-scale controlled trial of the use of chemotherapy as an adjuvant to surgical operation in women in whom cancer had already spread. This study was carried out by the National Surgical Adjuvant Breast Project (NSABP), headed by Dr. Bernard Fisher. Half of the women were given

L-phenylalanine mustard (L-Pam®) after radical mastectomy and half were given a placebo.[2] Treatment failures occurred in 22 percent of 108 patients receiving placebo and in 9.3 percent of 103 women given L-phenylalanine mustard. This difference was only statistically significant for premenopausal women and continued follow-up has shown no meaningful difference for women who are postmenopausal.

In 1973 Bonadonna at the National Cancer Institute of Milan began a study identical to Fisher's except that the chemotherapy was a three-drug combination called CMF (cytoxan, methotrexate, 5-fluorouracil), which had been found to be superior to L-phenylalanine mustard in advanced disease studies. In only 5.3 percent of 207 women who received CMF was there recurrence of cancer, as opposed to 24 percent of 179 women in whom surgical operation alone was done.[3] At the time these findings were reported the patients in the study had been followed for an average of only 14 months, although some had been observed for 27 months. In a further analysis made in April of 1976 the overall follow-up period from radical mastectomy was 17 months with an overall recurrence rate of 29.6 percent in the group treated only with surgical operation, as compared with 12 percent in the CMF-treated group. In women with four or more nodes, it was 47.1 percent for the control group, versus 16.4 percent for the CMF-treated patients. When the patterns of relapse were looked at the total difference in the incidence of local-regional relapse between the two treatment groups was 11.7 percent (21/179) for the control group, versus 2.4 percent (5/207) for the CMF-treated group, indicating a very high degree of local-regional control with the chemotherapy.[4]

Bonadonna[3] indicated that the "results should be considered with caution, since, at present the effects of this therapy on survival and possible long-term side effects remain unknown." He indicated that while the results were "promising" the optimism should be tempered by the consideration that it is too early to tell whether CMF therapy is merely delaying recurrence or actually lengthening survival. Since breast cancer is a chronic disease which may reappear as many as 20 years after initial surgical operation there is some validity to the above statement. Still Fisher[5] has shown in his ten-year analysis of his earlier Thiotepa adjuvant study that the diminished recurrence rate, in premenopausal women in whom four or more positive nodes are found, observed with Thio-tepa led to a survival gain at both five and ten years which correlated with diminished recurrence and was statistically significant. This study indicates a high probability that when five- and ten-year survival data are available a meaningful survival impact will be seen but only time will tell.

Despite the caution expressed it does appear that for the first time in a major cancer killer, well controlled randomized trials in breast cancer have demonstrated the soundness of the rationale for using prolonged surgical adjuvant chemotherapy. This has far-reaching implications for therapy in tumors in general and in breast cancer in particular.

These data now tend to downgrade the importance of arguments over the relative merits of one surgical procedure versus another. The lesser operations have been advocated for cosmetic purposes only and purely surgical trials have been testing the null hypothesis that less radical surgical procedures are as good as, but no better than, more radical ones. At this time, all modalities which have been considered for local and regional control must be evaluated and reevaluated in the light of findings indicating the effectiveness of a systemic agent. In essence, as systemic therapy becomes more effective it may become more likely that lesser surgical procedures could be comparable. However, it is critical that the nodal status of all patients be known since this is the strongest indication we now have for the applicability of systemic treatment. This requires that axillary staging be carried out, even if the patient has a segmental or total mastectomy.

The critical question facing a practicing clinician is what should he do for his patients today. While ideally one would like to have definitive long-term analysis available, therapeutic decisions have to be made today based on preliminary data. For Holland[6] the issue is clear cut. He considers the Bonadonna study of "monumental importance" and recommends the use of adjuvant chemotherapy. He states that "the risks of carcinogenesis, fatal drug intoxication and other morbidity are certainly much less hazard than the certain death that inexorably follows clinically evident metastatic cancer." On the other hand Constanza in the same journal states that "it is much too soon to regard chemoprophylaxis in breast cancer as a proven method of treatment." For now, she believes, it should not be under-

taken by nonresearch physicians. Currently all clinical trials sponsored by the National Cancer Institute utilize chemotherapy in all patients after mastectomy in whom positive nodes are found. The current "controls" are L-phenylalanine mustard or CMF. Clearly more clinical research is needed to fully delineate the optimal drug combination and the sequence and duration of use. Ideally all patients should be entered into research protocols. With the current state of oncologic practice this cannot be a reality. Practicing clinicians must weigh the evidence available and make the best judgment they can for patients. Nothing in medicine is fixed and the state of the art is always changing.

As has been stated by Fisher[7] the labeling of a study as "prospective" or "randomized" or as a "clinical trial" does not necessarily ensure the worth of the data produced. Prospective and randomized clinical trials are aimed at comparing two or more methods of treatment in similar groups of patients. For comparison of results of different trials it is mandatory that an exact description of categories be made available. When the critical variables of patient selection, experimental design, treatment regimens and evaluation of response are examined in studies being carried out at present, a significant lack of comparability is observed among them all. Some of the variations are the result of differing viewpoints on treatment potentials of the various modalities involved and some are due to differing definitions of clinical variables. The ways that surgical procedures, chemotherapy, immunotherapy and radiotherapy can be combined in the treatment of breast cancer are so manifold that it will be impossible to test more than a small fraction of all the combinations and sequences. However, it is crucial that the data resulting from these and other studies be sufficiently comparable so that future studies can be rationally planned and patient resources used as efficiently as possible. Unless all investigators are able to agree upon definitions in the basic standards of design the vicissitudes of performance will lead to inconsistent results that will only continue the controversies about the optimal therapy of breast cancer.

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REFERENCES

1. Carter SK: Integration of chemotherapy into combined modality treatment of solid tumors—VII. Adenocarcinoma of the breast. Cancer Treatment Reviews 3:111-114, 1976.

2. Fisher B, Carbone P, Economou SG, et al: 1-Phenylalanine mustard (L-Pam) in the management of primary breast cancer. N Engl J Med 292:117-122, Jan 16, 1975

3. Bonadonna G, Brusamolino E, Valagussa P, et al: Combination chemotherapy as an adjuvant treatment in operable breast cancer. N Engl J Med 294:405-410, Feb 19, 1976

4. Rossi A, Valagussa P, Bonadonna G: Surgery and adjuvant chemotherapy in the treatment of operable breast cancer. (Submitted for publication)

5. Fisher B, Slack N, Katrych D, et al: Ten year follow-up results of patients with carcinoma of the breast in a co-operative clinical trial evaluating surgical adjuvant chemotherapy. Surg Gynecol Obstet 140:528-534, 1975

6. Holland JF: Major advance in breast-cancer therapy (Editorial). N Engl J Med 294:440-441, Feb 19, 1976

7. Fisher B: Cooperative clinical trials in primary breast cancer: A critical appraisal. Cancer 31:1271-1286, 1973